

What is claimed is:

1. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating a library of virtual compounds *in silico* according to defined criteria, and evaluating *in silico* the binding of said virtual compounds with said target nucleic acid according to defined criteria.
5
2. A method of defining a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising generating *in silico* a plurality of virtual oligonucleotides according to defined criteria, and evaluating *in silico* the binding of said plurality of virtual oligonucleotides with said target nucleic acid according to defined criteria.
10
3. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid comprising, generating *in silico* a library of virtual compounds according to defined criteria wherein said virtual compounds modulate the expression of said target nucleic acid sequence, and robotically synthesizing synthetic compounds corresponding to at least some of said virtual compounds.
15
4. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid comprising generating *in silico* virtual compounds according to defined criteria wherein said virtual compounds modulate the expression of said target nucleic acid sequence, synthesizing synthetic compounds corresponding to at least some of said virtual compounds, and robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties.
20
5. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating *in silico* a library of nucleobase sequences according to
25
30

defined criteria and evaluating *in silico* a plurality of virtual oligonucleotides having said nucleobase sequences according to defined criteria.

6. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising evaluating *in silico* a plurality of virtual compounds according to defined criteria and robotically synthesizing a plurality of synthetic compounds corresponding to said plurality of virtual compounds.
- 10 7. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising evaluating *in silico* a plurality of virtual compounds according to defined criteria and robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.
- 15 8. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating a library of nucleobase sequences *in silico* according to defined criteria and robotically synthesizing a plurality of synthetic compounds having said nucleobase sequences.
- 20 9. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising robotically synthesizing a plurality of synthetic compounds and robotically assaying said plurality of synthetic compounds for one or more desired physical, chemical or biological properties.
- 25 10. A method of defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating a library of nucleobase sequences *in silico* according to

defined criteria and robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties.

5 11. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

10 (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and

(c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

15 12. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

20 (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and

(c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

25 13. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

30 (b) robotically synthesizing a plurality of synthetic oligonucleotides having at least

some of said nucleobase sequences; and

(c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

5 14. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;

10 (b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

(c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

15 15. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

20 (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria;

(c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

25 (d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

16. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

30 (a) generating a library of nucleobase sequences *in silico* according to defined criteria;

- (b) choosing an oligonucleotide chemistry;
- (c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step (a) and said oligonucleotide chemistry of step (b);
- 5 (d) robotically assaying said set of synthetic oligonucleotides of step (c) for a physical, chemical or biological activity; and
- (e) selecting a subset of said set of synthetic oligonucleotides of step (c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds.

10 17. A method of generating a set of oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- 15 (b) choosing an oligonucleotide chemistry;
- (c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) and the oligonucleotide chemistry of (b) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;
- 20 (d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step (c) and said oligonucleotide chemistry of step (b);
- (e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity; and
- 25 (f) selecting a subset of said set of synthetic oligonucleotides of step (d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

30 18. The method of claim 12, wherein said step of robotically assaying said plurality of synthetic oligonucleotide compounds is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

19. The method of claim 11, wherein said target nucleic acid sequence is that of a genomic DNA, a cDNA, a product of a polymerase chain reaction, an expressed sequence tag, an mRNA or a structural RNA.

5 20. The method of claim 11, wherein said target nucleic acid sequence is a human nucleic acid.

10 21. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising generating a library of antisense nucleobase sequences *in silico* according to defined criteria.

15 22. A method of identifying a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria.

20 23. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an compound to said nucleic acid sequences comprising robotically synthesizing a plurality of synthetic antisense compounds.

25 24. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an compound to said nucleic acid sequences comprising robotically assaying a plurality of synthetic antisense compounds for one or more desired physical, chemical or biological properties.

30 25. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising generating *in silico* a library of nucleobase sequences according to defined criteria and evaluating *in silico* a plurality of virtual oligonucleotides having said nucleobase sequences according to defined criteria.

26. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria and robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides.

5

27. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria and robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

10

28. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising generating a library of nucleobase sequences *in silico* according to defined criteria and robotically synthesizing a plurality of synthetic oligonucleotides having said nucleobase sequences.

15

29. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising robotically synthesizing a plurality of synthetic oligonucleotides and robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

20

30. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising generating a library of nucleobase sequences *in silico* according to defined criteria and robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties.

25

31. A method of identifying one or more nucleic acid sequences amenable to antisense

30

binding of an oligonucleotide to said nucleic acid sequences comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

5 (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and

(c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

32. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

10 (a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and

15 (c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

33. A method of identifying one or ~~more~~ nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

20 (a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences; and

25 (c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

34. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

30 (a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;

(b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

(c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

5

35. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria;

(c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

(d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

36. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) choosing an oligonucleotide chemistry;

(c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step (a) and said oligonucleotide chemistry of step (b);

(d) robotically assaying said set of synthetic oligonucleotides of step (c) for a physical, chemical or biological activity; and

(e) selecting a subset of said set of synthetic oligonucleotides of step (c) having a desired level of physical, chemical or biological activity.

37. A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined

criteria;

- (b) choosing an oligonucleotide chemistry;
- (c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;
- 5 (d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step (b) and said oligonucleotide chemistry of step (c);
- (e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity; and
- 10 (f) selecting a subset of said set of oligonucleotides of step (d) having a desired level of physical, chemical or biological activity.

38. The method of claim 32, wherein said step of robotically assaying said plurality of synthetic antisense oligonucleotides is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

39. The method of claim 31, wherein said nucleic acid sequence is that of a genomic DNA, a cDNA, a product of a polymerase chain reaction, an expressed sequence tag, an mRNA or a structural RNA.

40. The method of claim 31, wherein said nucleic acid sequence is a human nucleic acid.

25 41. A computer formatted medium comprising computer readable instructions for identifying compounds that have one or more desired properties according to defined criteria and that bind to a genomic DNA, a cDNA, a product of a polymerase chain reaction, an expressed sequence tag, an mRNA or a structural RNA.

30 42. A computer formatted medium comprising computer readable instructions for performing the method of any one of claims 1 to 20.

43. A computer formatted medium comprising computer readable instructions for performing a method of identifying one or more nucleic acid sequences amenable to antisense binding of a compound to said nucleic acid sequences.

5 44. A computer formatted medium comprising computer readable instructions for performing the method of any one of claims 21 to 40.

10 45. A computer formatted medium comprising one or more nucleic acid sequences amenable to antisense binding of a compound to said nucleic acid sequences in computer readable form.

15 46. A computer formatted medium comprising one or more nucleic acid sequences amenable to antisense binding of a compound to said nucleic acid sequences in computer readable form, wherein said one or more nucleic acid sequences is identified according to the method of any one of claims 21-40.

20 47. A process for validating the function of a gene or the product of said gene comprising generating *in silico* a library of nucleobase sequences targeted to said gene and robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for effects on biological function.

25 48. A process for validating the function of a gene or the product of said gene, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and

(c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

30 49. A process for validating the function of a gene or the product of said gene,

comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- 5 (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and
- (c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for effects on biological function.

50. A process for validating the function of a gene or the product of said gene, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- 10 (b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences; and
- 15 (c) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

51. A process for validating the function of a gene or the product of said gene, comprising the steps of:

- 20 (a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;
- (b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and
- 25 (c) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

52. A process for validating the function of a gene or the product of said gene, comprising the steps of:

- 30 (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase

sequences of (a) according to defined criteria;

(c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

5 (d) robotically assaying said plurality of synthetic oligonucleotides for effects on biological function.

53. A process for validating the function of a gene or the product of said gene, comprising the steps of:

10 (a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) choosing an oligonucleotide chemistry;

(c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step (a) and said oligonucleotide chemistry of step (b);

15 (d) robotically assaying said set of synthetic oligonucleotides of step (c) for effects on biological function; and

(e) selecting a subset of said set of synthetic oligonucleotides of step (c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds.

20 54. A process for validating the function of a gene or the product of said gene, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) choosing an oligonucleotide chemistry;

25 (c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) and the oligonucleotide chemistry of (b) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

30 (d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step (c) and said oligonucleotide chemistry of step (b);

(e) robotically assaying said set of synthetic oligonucleotides of step (d) for effects

on biological function; and

(f) selecting a subset of said set of synthetic oligonucleotides of step (d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

5

add
Ad